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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,497	02/17/2000	DAVID J. FITZGERALD	015280-317100US	4036

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,497	FITZGERALD ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-11,13,14,16,17,22-26,29-32 and 50-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-11,13,14,16,17,22-26,29-32 and 50-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/04/05 has been entered.

2. Claims 50-55 have been added.

3. Claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32 and 50-55 are under examination.

4. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

5. The following Office Action contains NEW GROUNDS of rejections.

Response to Arguments

6. The rejection of claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32 and newly added claims 50-55 under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988) and Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989), Cabilly et al (U.S Patent 4816567, issued 3/89), Boss et al (U.S Patent 4816397, issued 3/89), Robinson et al (U.S. Patent 5618920, filed 4/94),

Ward et al (Nature 341:544-546, 1989), and Huston et al (U.S. Patent 5258498, issued 11/93) is maintained.

The response filed 3/4/05 has been carefully considured but is deemed not to be persuasive. The response states that the federal circuit has held that DNA sequence is not obvious over general methods of isolating cDNA or DNA and cites *In re Deuel* and further the response states that the cited references teach only PCR methods for obtaining VH and VL and they do not teach a particular sequence and further there is no suggestion in Shan et al that the hybridoma would produce the "RFB4" antibody with the precise sequence of SEQ ID NO:1 (see page 8 of response).

In response to this argument, the art cited for PCR does demonstrate that it is routine in the art to obtain the DNA and amino acid sequence of the VH and VL of any hybridoma contrary to In re Deuel. In In re Deuel the specific facts are different from those of an antibody hybridoma. While it may be unobvious to obtain just any DNA from a particular cell, the obtaining of the DNA sequence from a hybridoma for the VH and VL is routinely done as evidenced from the prior art. In addition, the art of Shan et al specifically teaches hybridoma cell line of RFB4 and cites Campana et al for the culturing of the cell line. Thus, Shan does teach the hybridoma. In addition, the Shan reference was from the Royal Free Hospital in London which as evidenced from Mansfield et al (Blood 90:2020-2026, 1997), which is the inventors own work describing the invention, states that the RFB4 IgG-producing hybridoma was from the Royal Free Hospital in London (see page 2020 last 2 lines of right column). Thus, one skill in the art would conclude that the hybridomas were the same. In addition, absence evidence

to the contrary the hybridoma was available and given to others as indicated by Shan et al.

The response further states that as explained in the FitzGerald Declaration mailed 3/11/04 one could not have predicted the high level of expression, retention of parental IgG binding affinity, superior toxicity of the RFB4 immunoconjugates of the invention and cites work with the LL2 antibody and states that the scFv and the dsScFv were less stable and one could not predict which antibody sequence will express well or be stable and this is evidenced from Kreitman and Pastan (Sem in Cancer Biol 6:297, 306, 1995 and cited page 303 (see page 8 of response).

In response to this argument, Reiter et la (Biochemistry) specifically teach they have optimized the design and the purification scheme so the yields of dsFv-active immunotoxins are consistently higher than those of the scFv-toxins and can get up to 70 mg per liter and the increased yield is due to the decreased tendency of properly folded immunotoxins to aggregate (see abstract). Thus, it would not have been surprising to get higher expression or production of the dsFv-toxins. In addition, Reiter et al (Nature Biotech cited by applicant) teach 4 out of 8 dsFv-immunotoxins had improved binding affinity (see page 1243, left column). The Reiter et al (Biochemistry) clearly shows better cytotoxicity for the dsFV as compared to the scFv and better expression yields (see Table 1) and better stability (see Table 2) and teach "that dsFv's have at least the same binding properties as scFv's, and in some cases they may be better" (see abstract) and Reiter et al teach that scFv can retain the specificity and affinity of IgG (see page 5451). In addition, because the dsFv have superior characteristics over the

scFv they would obviously be chosen over scFv and in addition Shen et al teach that the Fab'-RFB4 bound 1.2 to 3.5 times more stronger than other Fab' fragments and the potent cytotoxic activity of the RFB4-AS appears to derive from their superior binding affinity and the art recognizes the superiority of this antibody. With regard to the Krietman et al reference, this reference demonstrates only one instant where the dsFv had low activity, however, in all of Reiter et al (Biochemistry) and Kuan et al (Biochemistry) the dsFv were active and potent and as such one skill in the are would have a reasonable expectation of success in making the claimed immunoconjugate dsFv with the RFB4 antibody.

Therefore, the prior art teach increased production, better toxicity, retention of affinity for the dsFv-toxins and as such one skill in the art would expect the RFB4-toxin to have such properties.

Newly added claims 50-55 are obvious because an dsFv of RFB4 would have a sequence that is 100% identical to SEQ ID NO:2 and 4 and would bind with the same affinity as the prototype. In addition, the references do teach an expression cassette and host cell for expression.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 50-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant immunotoxin comprising SEQ ID NO:2 and 4 and a cysteine at position 100 and 44 wherein the immunotoxin binds CD22 and comprises a toxin of PE38 and an expression cassette and host cell comprising DNA encoding such immunotoxin, does not reasonably provide enablement for a recombinant immunotoxin comprising a sequence that is 95% to SEQ ID NO:2 and 4 and a cysteine at position 100 and 44 wherein the immunotoxin binds CD22 with greater than 90% affinity of the prototype RFB4 dsFv and comprises a toxin of PE38 and an expression cassette and host cell comprising DNA encoding such immunotoxin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a recombinant RFB4 dsFv immunotoxin with any alterations in the CDRs of the antibody. The specification teaches the RFB4 dsFv as having SEQ ID NO:2 and 4 and does not teach any antibody as broadly claimed which encompasses antibodies with altered CDR amino acids.

The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding

myeloma protein resulted in the loss of antigen-binding function. It is unlikely that dsfv antibodies as defined by the claims which may contain alterations anywhere including the CDRs, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. In addition, Colman (Research in Immunology 145:33-36, 1994) teach that in antibody-antigen binding interactions the above examples paint a confusing picture because even a very conservative substitution may abolish binding (see page 35). Therefore, one skill in the art would not conclude that an antibody that contained 90% to SEQ ID NO:2 or 4 with alterations in the CDRs would have the required binding specificity.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention

Conclusions

9. No Claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by

telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 571-273-8300.

Larry R. Helms

571-272-0832